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Is schizophrenia a neurodevelopmental disorder?

A well established fact about schizophrenia is that first degree relatives have an increased risk of the disorder. Few now doubt that schizophrenia has a genetic basis, yet its mode of inheritance has to be explained. Even the identical twin of a schizophrenic stands a better than 50% chance of escaping the illness.[1] Genetic factors are not the whole story.

Kraepelin, who derived the concept of schizophrenia, considered that both heredity and organic brain disease were implicated, but somehow the organic aspects were neglected until the publication of a study using computed tomography by Johnstone *et al* in 1976.[2] A decade of such research has confirmed that the cerebral ventricles or cortical sulci are enlarged in many schizophrenics. Such changes are non-specific and can follow head injury, intracranial infections, and alcoholism and other cerebral insults.[3] As they are present in the earliest stage of schizophrenia and are not progressive they may be the sequelae of earlier events of aetiological importance. But what events—and how early?

The epidemiology of schizophrenia probably still holds the key. The disorder generally begins in early adult life, but the peak incidence in men is nearly a decade earlier than that in women.[4] The reason for this is unclear. An equally puzzling but equally consistent finding is the small excess of births of schizophrenics in the cold winter months.[5] This excess is not shared by the siblings of schizophrenics and is greater in those without a family history and in men with paranoid illness.[6,7] The most likely explanation is that some environmental factor associated with winter birth causes neural damage in the fetus or neonate.

The cause could be a viral infection or a seasonal difference in other complications that occur during pregnancy or delivery.[8,9] Schizophrenics seem more likely than controls to have a history of obstetric complications,[10,11] and, despite the various events encompassed by the term, obstetric complications may increase the risk of schizophrenia. Furthermore, increased ventricular size and other abnormalities seen on computed tomography are more common in those schizophrenics with a history of obstetric complications.[12]

Much research implicates the left rather than the right cerebral hemisphere in schizophrenia.[13] There is evidence that schizophrenics are more likely to be left handed than controls,[14] and possibly the normal development of lateralised cerebral dominance can be disrupted by premature birth with a resultant increase in left handedness.[15]

What mechanism could explain the relation between obstetric complications, abnormalities on computed tomography, and schizophrenia? The early development of the central nervous system is characterised not only by cellular proliferation and neuronal migration but also by cell death.[16] Complications during pregnancy and at birth can interfere with this neuronal fallout and impair the organisation of axonal connections, which leads to immature patterns of cells and their projections persisting.[16] Recent neuropathological findings in schizophrenia are suggestive of such neuronal damage early in life.[17,18]

In addition, imaging techniques have shown that about half of premature infants suffer intraventricular or periventricular haemorrhage. Most of these small bleeds are of little consequence, but in some cases regions of periventricular necrosis ensue that may cause non-progressive enlargement of the lateral and third ventricles.[19] Infants with ventricular enlargement have been followed up only to an age of 6 or 7 years, but it is already clear that they have an increased risk of abnormalities of tone and reflexes, and minor deficits in perceptual and cognitive skills.[20] Although studies following up preterm babies to adolescence cannot yet rely on radiological evidence of intraventricular haemorrhage at birth, the growing children already show various cognitive and behavioural disorders.[21] Soft neurological signs and cognitive impairment are, of course, found in some schizophrenics.

None of this explains why a lesion incurred in the first few months of life should increase the likelihood of psychosis some two decades later. A latent period between obstetric complications and their sequelae has, however, been noted in epilepsy and dyskinesias.[22] A latent period has also been described after experimental lesions in animals, which despite being made at or before birth do not cause obvious behavioural disturbances for several years. This is the case for prenatal dorsolateral frontal lesions in primates.[23] A similar process may account for the onset of schizophrenic symptoms—that is, the lesion lies dormant until the brain matures sufficiently to call into operation the damaged systems.[24] The greater vulnerability of the male brain to early damage as well as differential rates of myelination could explain the earlier onset of schizophrenia in men.

Schizophrenia is not an obstetric disease, but increasing evidence shows that impaired neural development is important in some cases. Certainly, there now exists a plausible mechanism whereby complications in pregnancy and at birth can not only translate into lasting alterations in neuronal circuits but also produce patterns of brain injury

highly reminiscent of those reported in some schizophrenics.

Hitherto it has been difficult to acount for the excess of births in winter or the sex difference in age of onset in schizophrenia. Similarly, arguments over the importance of soft neurological signs, cognitive impairment, and abnormalities of laterality have not been resolved. But a model that regards early neurodevelopmental deviance as one of several risk factors does provide a unifying explanation for what until now have been regarded as curious epiphenomena of schizophrenia.

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District cancer physicians: integration or fragmentation?

Health services change in response to shifts in the demographic and social structure of populations, movements in the size of disease pools, advances in medical technology, increases in public awareness and expectations, and alterations in resources. They are also influenced by the way professions seek to group their skills. These groupings can lead generalists to relinquish patients to specialists and alter the way in which different specialties see their responsibilities. These issues are raised by a proposal from a working party of the Association of Cancer Physicians that a network of cancer physicians should be established.[1] The proposal is that the physicians should have appointments either within district general hospitals or (if distance and population size preclude it) at a regional cancer centre, from which they would deliver a visiting service.

Without a strong medical oncology service in districts the working party thinks that some patients with malignant disease could receive unnecessary or inappropriate chemotherapy, fail to be treated with cytotoxic drugs when they should be, or receive inadequate dosages or regimens that depart from established protocols. The district cancer physician should remedy these deficiencies and also encompass other aspects of care such as supporting the families of patients with cancer and taking responsibility for the district's terminal care facility.

If such a proposal were to be implemented one repercussion would be on the consultant expansion programmes of regional health authorities—the working party envisages 63 posts in England and Wales. Another repercussion would be on the drug budgets of district health authorities: cytotoxic drugs could add so substantially to a hospital's annual expenditure that the district budget would be jeopardised. Health authorities are thus likely to be wary of this proposal. But when planning health services we should first consider the desired endpoint and only then consider the means of achieving it.

An earlier working party that deliberated on acute services for treating cancer described the ends succinctly[2]: "The underlying aim of cancer services should be to ensure that cancer patients, whether potential or confirmed, have speedy access to the diagnostic and treatment services their condition demands. . . . This must be the baseline on which the efficacy of services in any region is judged." The report went on to identify the hallmark of such a service as "integration." The Association of Cancer Physicians' report does not use this word, though a cap is doffed to it when medical oncology and radiotherapy are described as "complementary." Few would dispute that the medical oncologist has an important part to play in a modern cancer service, but so do radiotherapists, surgeons, gynaecologists, paediatricians, and haematologists. Moreover, some of these specialists are specialising still further, and we see the advent, for example, of surgical and gynaecological oncologists.

The concept of a district cancer physician as proposed is not fully consistent with the need to build within a well structured pattern of care. A preferable model would be a closer integration of clinical oncology and radiotherapy to provide strong specialist subregional centres of expertise that could then respond flexibly to the needs of the district general hospitals. Moreover, the idea that the district cancer physician might take responsibility for terminal care services and the suggestion that each district should have a designated oncology health visitor or district nurse could introduce too great a rigidity into local services.

The ground may, however, shift and force a reappraisal of the system. Ehrlich's magic bullet may be found, and we do not know what sort of doctor will be required to fire it and from what range.

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